DETAILED ACTION

1. Applicant's submission filed on March 28, 2008 has been entered. Claims 1, 10-13, 42-45 and 47-52 are pending and under examination.

Response to Amendment

2. The rejection of claims 1, 10-13, 42-45, 47 and 48 under 35 U.S.C. 103(a) as being unpatentable over Allaway *et al.* (5,817,767, "Allaway") in view of Bolognesi *et al.* (5,464,933, "Bolognesi") is withdrawn because the claims as amended require that the antibody bind CD4. Allaway's antibodies bind gp120. Therefore, the rejection is withdrawn in view of Applicant's amendment.

Claims Summary and Interpretation

3. The claims as amended are drawn to a composition comprising:

- A monoclonal antibody or a portion thereof that binds an epitope of CD4, thus retarding attachment of HIV-1 to a CD4+ cell by retarding binding of HIV-1 gp120 envelope glycoprotein to CD4; the antibody is either human, humanized, or chimeric; and,
- T-20 (SEQ ID NO: 1), which retards gp41 from adopting a conformation capable of mediating fusion of HIV-1 to a CD4+ cell by binding noncovalently to an epitope on a gp41 fusion intermediate.

The relative mass ratio of the compounds in the admixture ranges from about 100:1 to about 1:100, wherein the composition inhibits HIV-1 infection of the CD4+ cell. Also claimed are methods of inhibiting HIV-1 infection of a CD4+ cells by administering the claimed composition.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 10-13, 42-45, 47 and 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wang (US Patent 5,691,976) in view of Bolognesi *et al.* (5,464,933, "Bolognesi"). The claims are summarized above. Wang discloses monoclonal anti-CD4 antibodies and antibody homologs (fragments, including Fab fragments) that are humanized or chimeric (col. 11, lines 36-53). The antibodies bind to CD4 and retard attachment (block binding) of gp120 to surface CD4 (col. 12, lines 41-44). Also disclosed are methods of administering the antibodies to a subject in combination with other therapeutics for the treatment of HIV infection (col. 19, lines 40-67). Wang does not specifically teach the use of T-20 in combination with the anti-CD4 antibodies. However, Bolognesi discloses that DP-178 (T-20, SEQ ID NO: 1) exhibits potent anti-HIV transmission activity (see abstract and col. 5, lines 19-29). It would have been obvious to combine the anti-CD4 antibody of Wang and the T-20 peptide of Bolognesi into a combination therapy composition and method of treatment. One would have been motivated to make this combination because it would result in a composition that targets multiple aspects of HIV infection, thus improving the treatment efficacy. As is commonly recognized in the art, evidenced by Wang's teaching that the antibodies may be used in combination with other HIV therapeutics, combination therapies for HIV infection are routine.

With regard to the relative mass ratios of Wang's antibody to Bolognesi's peptide, it is routine in the art and would have been well within the ability of the ordinary artisan to determine the ratio of compounds that would exhibit the desired effect of inhibiting HIV infection in a cell. Therefore, the invention would have been obvious to one of ordinary skill in the art at the time the invention was made.

Applicant's arguments have been carefully considered but fail to persuade. Applicant's substantive arguments are primarily directed to the following:

- Applicant argues that Wang's suggestion to combine anti-CD4 antibodies with other anti-HIV agents does not specifically address agents that bind to gp41. Applicant asserts that because the two agents employ different mechanisms for blocking fusion, one would not have a reasonable expectation of success that the two compounds would work together or compete with one another.
  - In response to Applicant's arguments, the Office recognizes that the structure and mechanism of action of Wang's antibody and a T-20 peptide are distinct. Wang's antibody target pre-fusion events, and the T-20 peptide targets a fusion intermediate. As in known in the art, evidenced by Wang, combination therapies are routine and desirable. In the event that Wang's antibody does not block every single HIV virion from binding to CD4, the other agent will inhibit the fusion intermediate. Addressing various aspects of HIV infectivity (binding and fusion, among other targets of HIV therapeutics) results in a multi-faceted approach, a common practice in the art of HIV therapy. The Office maintains its position that

it would have been obvious to the ordinary artisan to combine the two agents together in a combination therapy.

- Applicant argues that there is unexpected superiority attributable to the two peptidyl compounds recited in Applicant's claims. Applicants points to page 26, lines 8-10, which explains that the degree of synergy was quantified using the Combination Index (CI) method, wherein a CI value greater than 1 indicates antagonism, and a CI equal to 1 indicates a purely additive effect. A CI less than 1 indicates a synergistic effect. Applicant points to Figure 2, where potent synergies over broad ranges of inhibitor ratios and concentrations were observed, translating into 17-fold and 5-fold reductions in the amounts of monoclonal antibody and T-20, respectively, needed to achieve 95% inhibition of viral entry. Applicant notes that the average CI values in Figure 2 for 95%, 90% and 75% inhibition are 0.31, 0.36 and 0.47, respectively.
    - In response, the synergism that Applicant points to is with regard to an antibody that binds gp120 (CD4-IgG2, see page 3 of the specification, first full paragraph). The claims are now drawn to a construct having an antibody that binds CD4. The results from Figure 2 are particular to a construct that is not instantly claimed.
    - Further, even considering the results, a greater than additive effect is not necessarily sufficient to overcome a prima facie case of obviousness because such an effect can either be expected or unexpected. Applicants must further show that the results were greater than those which would have been expected from the prior art to an unobvious extent, and that the results are of a significant, practical advantage. In this instance, Applicant's background disclosure (page 6, second

paragraph) discusses the synergistic inhibition of HIV-1 entry using certain anti-env antibody combinations, anti-CD4 antibodies, or CD4 based proteins, etc. Given that in the art of HIV therapy, combination therapies using different targets are routine, and the observance of synergism is also routine, one would have a reasonable expectation that the combination of Wang's antibody that targets binding to CD4, and Bolognesi's T-20 that targets the fusion intermediate would work synergistically. Given the synergies observed with other combination therapies involving anti-CD4 antibodies, as taught in the specification, synergism in the instantly claimed embodiment is not unexpected.

Double Patenting

5. Claims 1, 10-13, 42-45, 47 and 48 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-15 of U.S. Patent No. 6,692,745 B2, for reasons of record. Applicant indicated that they may consider filing a terminal disclaimer later in prosecution should allowable claims be indicated.

Conclusion

6. No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stacy B. Chen whose telephone number is 571-272-0896. The examiner can normally be reached on M-F (7:00-4:30), alternate Fridays off,. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/Stacy B. Chen/ 6-09-2008
Primary Examiner, TC1600